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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
08/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/076,416	**Applicant(s)** RIEPING ET AL.	
	Examiner David J. Steadman	**Art Unit** 1656	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 July 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *20 July 2010*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *35-38*.
   Claim(s) rejected: *23,26-28,33 and 39-42*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/David J. Steadman/
Primary Examiner, Art Unit 1656

Continuation of 11. does NOT place the application in condition for allowance because: Claims 23, 26-28, 33, and 35-42 are pending in the application. Applicant's amendment to the claims after final rejection, filed on 7/20/10, is acknowledged and has been entered into the record. Applicant's request for reconsideration is acknowledged.

The terminal disclaimer filed on 7/20/10 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patents 7,759,094, 7,504,242, 6,759,218, and 7,205,131, has been reviewed and is accepted. The terminal disclaimer has been recorded.

The rejection of claims 23, 26, 28, 33, and 42 under 35 U.S.C. 103(a) as being unpatentable over Kikuchi (US Patent 5,932,453) in view of Shimizu (US Patent 5,445,948) and Chang (J Bacteriol 154:756-762, 1983; cited as reference V in the Form PTO-892 mailed on 10/19/05) is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See item [7] beginning at p. 3 of the Office action mailed on 4/29/09.

The rejection of claim 27 under 35 U.S.C. 103(a) as being unpatentable over Kikuchi in view of Shimizu and Chang as applied to claims 23, 25-26, 28, 33, and 42 above and further in view of Matsui (US Patent 4,391,907) is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See item [8] beginning at p. 5 of the Office action mailed on 4/29/09.

The rejection of claims 39-41 under 35 U.S.C. 103(a) as being unpatentable over Kikuchi in view of Shimizu and Chang as applied to claims 23, 25-26, 28, 33, and 42 above and further in view of Dunican (US Patent 6,586,214) is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See item [9] beginning at p. 6 of the Office action mailed on 4/29/09.

RESPONSE TO ARGUMENT: At p. 5 of the instant remarks, applicant addresses the reference of Shimizu, arguing that the examiner's assertion that Shimizu teaches that acetate generally inhibits growth of E. coli in culture is not true. According to applicant, Shimizu teaches a concentration above 17 g/L of acetate inhibits the growth of E. coli.

Applicant's argument is not found persuasive. Initially it is noted that applicant addresses the references of Shimizu and Chang individually, where the rejection is based on a combination of references. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's remarks addressing Shimizu, although applicant asserts that Shimizu teaches a concentration above 17 g/L acetate inhibits E. coli growth, it is noted that Shimizu teaches that it is preferable to control the acetate concentration in a culture medium to "6 g/liter or less" (column 4, lines 44-50), where the results of Shimizu indicate that 6 g/L of acetate is achieved at 10 hours of culturing (column 4, lines 42-43). Thus, Shimizu prefers to maintain acetate concentration at 6 g/L or less in the culture medium.

The examiner acknowledges that a generalized statement was made with respect to the teachings of Shimizu. However, the examiner's statement regarding acetate inhibiting growth of E. coli was not intended to suggest that any concentration of acetate inhibits growth of E. coli in culture. This is clearly borne out by the noted teachings of Shimizu. The examiner's reliance on Shimizu is based on Shimizu's teachings that culturing of E. coli for production of a desired product results in production of a growth inhibiting substance, i.e., acetate, and that at a certain concentration achieved during routine culturing of 10 hours or more inhibits E. coli growth (column 4). Shimizu suggests removing the acetate from the culture medium to enhance production of a desired product by culturing the E. coli (column 6). It should be noted that the L-amino acid production methods of Kikuchi (column 10, lines 44-45) and Matsui (column 4, lines 64-65) each uses an E. coli culturing time of greater than 10 hours and thus the teachings of Shimizu are relevant to the production methods of Kikuchi and Matsui.

Beginning at p. 5, bottom, of the instant remarks, applicant addresses the reference of Chang, arguing that only with hindsight reasoning would one combine the reference of Chang with Shimizu. Applicant argues that Chang's inability to explain feeble growth of E. coli on acetate produced by pyruvate oxidase is an indication of the unpredictable effects of genetic modification. Applicant further argues that Chang does not use L-amino acid production strains and it cannot be concluded that similar results could be achieved using a production strain.

Applicant's argument is not found persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Chang's inability to explain feeble growth of E. coli on acetate produced by pyruvate oxidase (p. 762, column 1) is irrelevant with respect to whether or not one of ordinary skill in the art would have been motivated to combine Chang with Shimizu and the other cited references. Chang acknowledges that pyruvate oxidase (poxB, encoded by poxB gene) produces acetate (p. 756, column 1, top) and suggests production of acetate can be blocked by an E. coli strain with an inactivated poxB gene (p. 762, column 1, top), which is undisputed by applicant. Shimizu teaches that acetate inhibits E. coli cell growth at a certain concentration during routine culturing. Thus, one would have been motivated to inactivate a poxB gene in the E. coli of Kikuchi or Matsui with a reasonable expectation of inactivating its

corresponding catalytic activity that results in acetate production, motivated by a desire to reduce acetate in the culture medium. Although applicant asserts that one cannot conclude that similar results would have been achieved in an L-amino acid production strain of Kikuchi or Matsui, applicant provides no rationale or line of reasoning to support this allegation. To the contrary, since the method of Kikuchi or Matsui uses an E. coli, one of ordinary skill in the art would have had a reasonable expectation that inactivating the poxB gene in the E. coli of Kikuchi or Matsui would have had the effect of inactivating its corresponding catalytic activity.

Beginning at p. 6, bottom, of the instant remarks, applicant argues that the pathway involving poxB is not the primary source for acetate production, citing to p. 6657, column 2 of the reference of Chang et al. (J. Bacteriol. 181:6656-6663, 1999).

Applicant's argument is not found persuasive. The examiner has reviewed the noted statement in applicant's reference, however, this statement does not appear to disclose either explicitly or implicitly that "the pathway in which poxB is involved is not the primary source of acetate in a cell" as alleged by applicant. Further clarification is requested as to how applicant has arrived at this conclusion.

Perhaps applicant's intention in citing this statement is to suggest that one of skill in the art would have inactivated a pta gene rather than poxB to reduce acetate accumulation in a culture medium. However, applicant's reference notes that a pta mutant exhibits a "large growth defect" relative to a wild-type E. coli (p. 6661, column 2), while the poxB mutant of Chang is disclosed as growing at a normal rate on acetate containing medium and attaining a normal cell density (p. 758, column 1). As such, one of ordinary skill in the art would have recognized that inactivating a poxB gene would not have an affect on growth rate or cell density and because Chang explicitly discloses that poxB polypeptide catalyzes formation of acetate (p. 756, column 1, top) and that most acetate production is blocked in strains with a deletion of a poxB gene (p. 762, column 1, top), one would have been motivated to use an E. coli with an inactivated poxB in the method of Kikuchi or Matsui.

At p. 7 of the instant remarks, applicant argues that while it was generally known that acetate may significantly lower yield and productivity in different processes involving microorganisms, this is not a particular problem of L-amino acid production and one of ordinary skill in the art would not have sought to lower acetate formation and certainly not by inactivating poxB.

Applicant's argument is not found persuasive. There is no evidence of record to support applicant's allegation that acetate accumulation in an E. coli culture medium is "not a particular problem of L-amino acid production". According to MPEP 716.01(b).II, "[t]he arguments of counsel cannot take the place of evidence in the record".

Moreover, based on the combination of references, one of ordinary skill in the art would have recognized that the culturing times of Kikuchi and Mitsui result in growth-inhibiting levels of acetate in the culture medium. According to Shimizu, longer culturing times result in greater accumulation of acetate, noting that 6 g/L acetate is reached at 10 hours and 17 g/L is reached at 18 hours (column 4, lines 42-44). According to Shimizu, it is preferable to maintain 6 g/L or less of acetate in the culture medium, where acetate concentration reaches 6 g/L at 10 hours of culturing of E. coli (column 4, lines 42-50). The method Kikuchi encompasses culturing of E. coli for a time of "from 16 to 72 hours" (column 10, lines 44-45) and the method Matsui encompasses culturing of E. coli for a time of 72 hours (column 4, lines 64-65), thus requiring time periods that reach undesirable growth-inhibiting levels of acetate as noted by Shimizu.

At least for these reasons and the reasons of record, the claimed method would have been prima facie obvious at the time of the invention.

The provisional obviousness-type double patenting rejection of claims 23, 25-28, 33, and 39-42 as being unpatentable over: 1) claim 22 of co-pending US non-provisional application 10/812,315, now abandoned; 2) claim 40 of copending Application No. 11/658,477, which has issued as US Patent 7,759,094, is withdrawn in view of the abandonment of the '315 application and the terminal disclaimer filed on 7/20/10.

The obviousness-type double patenting rejection of claims 23, 25-28, 33, and 39-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over: 1) claims 8 and 22 of US Patent 7,504,242; 2) claims 7 and 19 of US Patent 6,759,218; and 3) claim 4 of US Patent 7,205,131 is withdrawn in view of the terminal disclaimer filed on 7/20/10.

The provisional obviousness-type double patenting rejection of claims 23, 25-28, 33, and 39-42 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 27 of co-pending application 10/847,610 in view of Kramer (J. Biotechnol. 45:1-21, 1996; cited in the PTO-892 filed on 4/20/04), Grabau (J. Bacteriol. 160:1088-1092, 1984; cited in the 9/3/02 IDS), Chang et al. (J Bacteriol 154:756-762, 1983; cited in the PTO-892 filed on 10/19/05; "Chang1"), and Chang et al. (J. Bacteriol. 167:312-318, 1986; cited in the IDS filed on 9/3/02; "Chang2") is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See item [12] beginning at p. 7 of the Office action mailed on 11/20/09.

Claims 35-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you

would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.